REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments, remarks, and enclosures herewith.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 1, 4-15 and 17-79 are now pending. Claims 1, 10-13, 15 and 20 have been amended, claims 2, 3 and 16 have been cancelled herein, and new claims 78 and 79 have been added, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims and the remarks herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments and remarks are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE OBJECTION TO THE CLAIMS IS OVERCOME

Claim 15 was objected to as containing non-elected subject matter. The objection is respectfully traversed.

The claims have been amended herein such that claim 15 now relates only to an isolated polypeptide in accordance with the elected subject matter. Reference to nucleic acid molecules, vectors, and host cells have been removed. Accordingly, the non-elected subject matter has been removed from the claim.

Reconsideration and withdrawal of the object to claim 15 is therefore respectfully requested.

III. THE REJECTION UNDER 35 U.S.C. §101 IS OVERCOME

Claims 1-3, 10, 11, 15 and 16 were rejected under 35 U.S.C. §101 as allegedly constituting non-patentable subject matter as the claims read on a product in nature. The rejection is respectfully traversed.

The claims have been amended herein to recite that the claims polypeptide or ligand are "isolated". Accordingly, the claims as presented herein do not read on subject matter found in nature, rendering the rejection moot.

Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. §101 are respectfully requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §112 ARE OVERCOME

Claims 1-3, 11-13, 15 and 16 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly lacks enablement for all of the claimed elements. The rejection is respectfully traversed.

Specifically, the Office Action alleges that the specification lacks enablement for fragments, other polypeptides having an antigenic determinant in common with SEQ ID NOs: 16, 26, 20 or 22 or functions equivalents thereof, and antibodies which specifically bind the fragments and equivalents. However, the Office Action admits that the specification is enabled for the full length polypeptides of SEQ ID NOs: 16, 26, 20 and 22, and isolated antibodies which specifically bind the full length polypeptide.

35 U.S.C. §112, first paragraph, requires that the specification describe how to make and use the invention. 35 U.S.C. §112, first paragraph, recites, in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]

A patent claim is invalid if it is not, *inter alia*, supported by an enabling disclosure. The test for enablement requires a determination of whether any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, (Fed. Cir. 1988). The factors involved in determining whether there is sufficient evidence to support a finding of enablement include, among others, (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed

to make or use the invention based on the content of the disclosure. *See Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404.

Applying the law to the instant facts, claims 1-3, 11-13, 15 and 16 are enabled. The pending claims relate to an isolated polypeptide, which polypeptide i) comprises or consists of the amino acid sequence as recited in SEQ ID NO:16 or SEQ ID NO:26; or ii) consists of the amino acid sequence as recited in SEQ ID NO:20 or SEQ ID NO:22 or consists of a combination of the amino acid sequences as recited in SEQ ID NO:4 and SEQ ID NO:6; or iii) is a fusion protein comprising a polypeptide according to i) or ii) or comprising a fragment of a polypeptide according to i) or ii) fused to a heterologous polypeptide; or iv) is a functional equivalent of (i) or (ii) or (iii), characterised in that it is homologous to the amino acid sequence as recited in SEQ ID NO:16 or SEQ ID NO:26 and has activity as an antagonist of cytokine expression and/or secretion.

The Office Action states that "[t]he art teaches that substitution of as little as a single amino acid will alter protein function" and relies on Ju *et al.* and Ledeman *et al.* as examples. Office Action at 5. According to the Office Action such unpredictability in the art, and the alleged failure of the specification "to provide any guidance as to how to make or use 'fragments' or mutated polypeptides with similar antigenic determinants which retain the function of the full length polypeptide" would require the skilled artisan to perform undue experimentation in order to use the claimed invention. Office Action at 5-6. Applicants respectfully disagree.

Initially, the term "antigenic determinant" has been removed from claim 1 and has been replaced by reference to an "immunogenic epitope". It is respectfully submitted that one of skill in the art will fully recognize and understand this phrase, such that no further teachings in the specification as to how to identify such an immunogenic epitope are required.

Furthermore, contrary to the assertions in the Office Action, the specification does provide guidance as to how to make and use fragments that retain the cytokine antagonist function of the full-length polypeptide and fragments of homologues that retain this function. Specifcially, Applicants respectfully direct the Examiner's attention to the specification at page 24, line 15 to page 25, line 3 which discloses that functionally equivalent polypeptides can be identified using the Inpharmatica Gene Threader.

The Inpharmatica Gene Threader allows highly accurate predictions of protein function to be made that were not possible using conventional methods. This system has been used to correctly annotate the function of many proteins to date. In contrast to conventional tools, the in-house system developed by Inpharmatica is based on the evaluation of *sequence* homologies, *structural* homologies and other relationships (such as taxonomical information) in a sophisticated manner. This highly sophisticated system is not, therefore, comparable with the basic tools previously known in the art. Unlike previous methods, the Inpharmatica Gene Threader assigns function reliably.

Furthermore, the examples in the application provide the skilled artisan with details of cytokine antagonist assays. It would not require undue burden for the skilled person to test fragments of the INSP052 polypeptide or homologues thereof identified as potential cytokine antagonists using the Gene Threader to confirm that they act as cytokine antagonists.

The application as filed also teaches the skilled person to identify fragments that contain an immunoglobulin domain (page 8 of the application as filed) and the functional importance of this domain (page 16, line 4-9 of the application as filed). The extracellular domain of the INSP052 polypeptide contains an immunoglobulin domain and the data presented in the examples confirm that extracellular fragments retain the activity of the full-length polypeptides. Indeed, fragments consisting of the extracellular domain or of exons 2 and 3 of the INSP052 polypeptide are fully enabled by the specification since they are specifically disclosed on pages 10-11, in Example 2 and in Figure 6 of the application as filed.

Indeed, the Examiner is reminded that the need for extensive experimentation is negated when the the skilled artisan is provided with the tools and techniques to make and use the invention as claimed. Accordingly, the disclosure of the use of the Inpharmatica Gene Threader in the making and use of the present invention should be considered as a factor in favor of the enablement of the specification.

Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

Claims 15, 16, 20 and 21 were also rejected under 35 U.S.C. §112, first paragraph because the specification allegedly lacks enablement for all of the claimed elements. The rejection is respectfully traversed.

Specifically, the Office Action alleges that the specification lacks enablement for "treating or diagnosing all diseases". Office Action at 6.

The claims have been amended herein such that they now refer only to inflammatory disease, autoimmune disease, liver disease or liver failure. As the examples in the specification provide information relating to the effects of altered cytokine levels on these diseases, the specification is enabled as to inflammatory disease, autoimmune disease, liver disease and liver failure.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

Claims 10-16, 20 and 21 were rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. The rejection is respectfully traversed.

As described above, the specification provides ample guidance as to those species which are encompassed by the currently pending claims. Specifically, the specification does provide detailed guidance as to how to make and use fragments that retain the cytokine antagonist function of the full-length polypeptide and fragments of homologues that retain this function. Again, Applicants respectfully direct the Examiner's attention to the specification at page 24, line 15 to page 25, line 3 which discloses that functionally equivalent polypeptides can be identified using the Inpharmatica Gene Threader. By providing those of skill in the art with the tools with which to identify the claimed species, the species have been adequately described in the specification. The species are described by their functionality, and a determinant of that functionality is provided in the form of the Inpharmatica Gene Threader. In addition, assay methods are provided which allow for the determination of whether candidate fragments act as cytokine antagonists, one of the described features of the claimed species.

Therefore, as the Applicants have adequately defined the claimed species, and provided the teaching needs to identify members of the species, the specification provides adequate written description. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-3, 10-16, 20 and 21 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejection is respectfully traversed.

Specifically, the phrases "antigenic determinant" and "increases or decreases the level of expression or activity of a polypeptide" were considered indefinite.

The claims have been amended herein to remove the phrase "antigenic determinant" and to qualify the phrase "increases or decreases the level of expression or activity of a polypeptide" as being in relation to the level of expression or activity of the polypeptide in the absence of the compound. Accordingly, the rejection is now moot.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, are respectfully requested.

V. THE REJECTIONS UNDER 35 U.S.C. §102 ARE OVERCOME

Claims 1, 2, 3, 10-16, 20 and 21 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Baughn et al. (WO 02/40671). Claims 103 and 12-14 were additionally rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Edwards et al. (U.S. Patent No. 6,783,961). The rejections are traversed and will be addressed in turn.

It is respectfully submitted that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure of the claimed invention. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990).

Baughn *et al.* discloses six proteins, termed IGSFP1-6. One of these, IGSFP-4, is alleged in the Office Action to be identical with amino acids 1-240 of the INSP052 polypeptide of SEQ ID NO:16 disclosed in the current application.

Taking each portion of amended claim 1 in turn, Baughn *et al.* clearly fails to contain all of the elements of any portion of the claim.

Baughn *et al.* does not disclose the amino acid sequence "comprising" or "consisting" of SEQ ID NO:16 or SEQ ID NO:26, as claimed in part i) of amended claim 1.

Furthermore, Baughn *et al.* does not disclose the existence of an extracellular domain in the IGSFP-4 polypeptide, let alone the sequence of this domain. It does not therefore disclose a polypeptide consisting of SEQ ID NO:20 or SEQ ID NO:22, as claimed in part ii) of amended claim 1.

The only disclosure of fusion proteins in Baughn *et al.* is a general statement on page 39 of the document that the full-length IGSFP-4 protein can be fused to other moieties to facilitate purification. There is no disclosure in Baughn *et al.* of fusing fragments of the IGSFP-4 protein to heterologous proteins, as claimed in part iii) of amended claim 1.

Additionally, Baughn *et al.* does not provide a detailed functional annotation of the IGSFP-4 protein, merely stating that it is a member of the "human immunoglobulin superfamily of proteins". Baughn *et al.* does not suggest that the full-length IGFSP-4 protein is a cytokine antagonist, nor that fragments of this protein will retain the ability to act as cytokine antagonists. The functional equivalents claimed in part iv) of amended claim 1 are thus novel over Baughn *et al.*

As Baughn *et al.* fails to teach or suggest all of the elements of any portion of claim 1, claim 1, and those claims depending therefrom, are necessarily patentable over Baughn *et al.* and the rejection must be withdrawn. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e) are respectfully requested.

Turning now to Edwards *et al.*, it is additionally clear that amended claim 1, and those claims depending therefrom, is also novel over Edwards *et al.*

Edwards *et al.* merely discloses thousands of unannotated EST sequences (SEQ ID NOs: 4101-8177), one of which is alleged in the Office Action to be similar to the INSP052 polypeptide. The sequence listing referred to in Edwards *et al.* was not published due to its length and the Office Action does not indicated which of the thousands of ESTs disclosed in Edwards *et al* it considers to be relevant to novelty. It has not therefore been possible for the applicant to verify the claim that this document discloses a protein that is identical to SEQ ID NO:16 from amino acids 1-58. Clarification is respectfully reqested.

In addition, contrary to the Office Action, Edwards *et al.* does not teach that any of the proteins encoded by the ESTs are cytokine antagonists. Column 60, lines 19-28, cited in the Office Action, merely indicates that proteins or polypeptides encoded by the ESTs "may be evaluated for anti-inflammatory activity" by looking at whether they increase or decrease cytokine levels. The mention of cytokine levels in column 60 is merely an invitation to the skilled person to test the thousands of polypeptides encoded by the ESTs. Edwards *et al.* discloses some 60 similar examples which suggest multiple different tests that may be carried out by the skilled person to try and determine the function of any polypeptide encoded by the ESTs.

The ESTs disclosed in Edwards *et al.* are too short to confer biological activity. Further, there is no indication in Edwards *et al.* of whether the ESTs are actually expressed in nature, let alone what the function of any expressed polypeptides corresponding to the ESTs may be or whether expressed polypeptides function as cytokine antagonists.

Edwards *et al.* does not disclose the full-length INSP052 polypeptide, a fragment of the INSP052 polypeptide consisting of the extracellular domain, fusion proteins containing fragments of the INSP052 polypeptide nor the fact that the INSP052 polypeptide and fragments thereof have cytokine antagonist activity. In contrast, the data presented in the current application show that the INSP052 polypeptide is a cytokine antagonist and that fusion proteins comprising the INSP052 extracellular domain act as cytokine antagonists and can be used to reduce liver damage in a mouse model of liver hepatitis.

Accordingly, as Edwards *et al.* fails to teach or suggest all of the elements of any portion of claim 1, claim 1, and those claims depending therefrom, are necessarily patentable over Edwards *et al.* and the rejection must be withdrawn. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) are respectfully requested.

VI. INFORMATION DISCLOSURE STATEMENT

The Examiner's attention is respectfully drawn to the documents listed on the accompanying PTO Form 1449. Copies of the references are enclosed.

This information disclosure statement is being filed after a first Office Action. Accordingly, the Commissioner is hereby authorized to charge $180.00 in payment of the fee set forth in 37 C.F.R. §1.17(p) to Deposit Account 50-0320.

It is respectfully requested that the Examiner considers and makes of record the documents cited herewith and that a copy of Form PTO-1449 be initialed by the Examiner and returned to the undersigned.

The filing of this Information Disclosure Statement is not an admission that the documents identified herein constitute prior art to the present application.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, prior to issuance of any paper other than a Notice of Allowance, an interview, is respectfully requested, with the Examiner and the

Examiner's supervisor, and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the amendments, remarks and enclosures herein, the application is in condition for allowance. Reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance, is respectfully requested.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: Thomas J. Kowalski by Angela M. Collison

Thomas J. Kowalski
Reg. No. 32,147
Angela M. Collison
Reg. No. 51,107
(212) 588-0800